Remarks

Claims 1-8 are cancelled. Claims 9-10 are amended to depend from newly added. Claims 11-12. Support for the claim amendments can be found throughout the specification. In particular support for "total blood cell RNA" is found throughout the specification and in particular is found at paragraph [0052], [0053] and paragraph [0055]. Support for the phrase "two or more gene differentially expressed" is found throughout the specification and in particular at paragraph [0060] and Figure 5. No new matter has been entered.

35 U.S.C. § 112 2nd Paragraph Rejections

Claims 4-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has removed the language asserted to be indefinite by canceling claims 4-8, and amending claims 9 and 10 to depend from newly added claims 11 and12.

In view of these claim amendments, Applicant respectfully requests withdrawal of the rejection.

35 U.S.C. § 102(b) Rejection

Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Jiang et al. (British Journal of Cancer, 1997, Vol. 75(6), pages 928-933), as evidenced by Expression Profile suggested by analysis of EST counts for gene alpha fetoprotein, downloaded 9/28/06, web site www.ncbi.nlm.nih.gov/UniGene/ESTProfileViewer.cgi?uglist=Hs51880 .

Anticipation requires that a prior art reference disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO*, Incorporated et al., 190 F.3d 1342, 1347 (Fed. Cir. 1999).

The office action states that Jiang et al teach a method of detecting and quantitating alpha-fetoprotein mRNA in a blood sample and comparing the level of alpha-fetoprotein in blood samples from various patients.

The claims as newly amended require detecting and quantitating two or more genes expressed in heart tissue in the recited blood samples, while the method described in the referenced Jiang et al. article comprises quantitating only one gene expressed in heart tissue in blood samples. Because the Jiang et al. reference does not teach all the claim limitations, specifically a method encompassing the quantification in blood of two or more genes expressed in heart tissue, Applicants contend the cited reference is not anticipatory. In view of the remarks and claim amendments, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al. (British Journal of Cancer, 1997, Vol. 76(5), pages 628-633),), as evidenced by Expression Profile suggested by analysis of EST counts for gene alpha fetoprotein, downloaded 9/28/06, web site www.ncbi.nlm.nih.gov./UniGene/ESTProfileViewer.cgi?uglist=Hs51880, and as evidenced by Expression Profile suggested by analysis of EST counts for gene albumin, downloaded 9/28/06, web site www.ncbi.nlm.nih.gov./UniGene/ESTProfileViewer.cgi?uglist=Hs418167.

The office action states that Wong et al teach a method of detecting alpha-fetoprotein and albumin mRNA in a blood sample, said mRNA being expressed in heart tissue according to the disclosed Expression Profile.

The methods recited in the claims as newly amended require identifying two or more genes and determining the amount of expression of an RNA corresponding to these genes in total blood cell RNA of blood samples which have not been fractionated into cell types. Unlike the amended claims, Wong does not teach measuring the amount of RNA expressed **in total blood cell RNA from blood samples which have not been fractionated into cell types**. Rather Wong teaches detecting RNA in fractionated blood samples – and more specifically teaches measuring the amount of RNA **from HCC cells.**

Wong in fact teaches that detecting RNA expressed in peripheral blood cells which cannot be attributable to HCC cells is a problem (see Introduction, second column, page 628) and thus teaches the development of "a semi quantitative estimation of the amounts of "hepatocyte-specific" mRNAs in the circulation of normal subjects and HCC patients for differential detection of **HCC cells** rather than normal **PMNCs**". As such, Wong et al. **teaches away** from measuring the differential expression of the amount of gene specific mRNA found in **total blood cell RNA from blood samples which have not been fractionated into cell types** and rather focuses on detecting mRNA in HCC cells as compared to a threshold level which is determined to be greater than the level of RNA detected as expressed in blood cells from fractionated blood samples. Because the Wong et al. reference does not teach all the claim limitations, specifically a method encompassing analysis of total blood cell RNA from blood samples which have not been fractionated into cell types, Applicants contend the cited reference is not anticipatory, and respectfully request withdrawal and reconsideration of the instant rejection.

35 U.S.C. § 112, 1st Paragraph Rejections

Claims 1-10 are rejected as failing to comply with the enablement requirement. Applicant respectfully traverses.

The office action relies on the specification to provide a use for the instant claims. In order to more clearly identify what Applicant is claiming, Applicant has amended the claims to clarify that Applicant is claiming a method of identifying biomarkers useful for diagnosing a disease of the heart, the biomarkers being limited to genes expressed in blood and in a heart tissue.

The office action states that it would require undue experimentation to practice the claimed invention. Applicants note that methods of identifying biomarkers were well known at the time of the invention. The point of novelty of Applicant's invention is identifying biomarkers which are differentially expressed in total blood cell RNA of test subjects vs. control subjects and one such utility of this methodology, as disclosed in the specification, is the application of this method to provide an indication of disease. Applicants contend that due to the ease of gene expression analysis in blood as compared

to tissue biopsies, and the well established statistical analysis applied to the determination of biomarkers, no undue experimentation is required.

The Examiner also points to the scope of the claims and notes that "the claims are extremely broad because they require only the comparison of a gene's expression in a single individual's blood to that of another single individual. The Applicant has in fact amended the claims so that the claims are directed to a method of identifying two or more genes that are differentially expressed, and requires the use of "samples from individuals having disease" and "samples from individuals not having disease". Thus,

. although the claims do not set forward a threshold of difference, it would be well understood to a person skilled in the art that when comparing samples as between these two groups, one is looking for a statistically significant difference.

The Examiner also argues, on the basis of post-filing art of Wu (2001) and Newton (2001), that many factors may influence the outcome of the data analysis and notes that conclusions depend on the methods of data analysis. While considerations such as variability, and normalization are of importance, these considerations are well understood by a person skilled in the art and have been applied for many years to permit development of biomarkers which are indicative of disease. These challenges are well understood, as are the routine experiments required to exemplify statistically significant differences in populations. These challenges do not detract from the fact that the Applicant has identified a novel method and is the first to teach the use of this method to measure differential expression of an RNA corresponding to two or more genes, where the RNA is measured in total blood cell RNA of blood samples which have not been fractionated into cell types.

Claims 2, 4, 5 and 10 are rejected as failing to comply with the written description requirement.

The office action contends that knowledge of genes which are heart tissue specific genes is required to practice the claimed invention, and that the specification does not describe which genes are differentially expressed in amounts detectable in the blood of individuals.

Applicant respectfully traverses, and notes that to meet the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.

This written description requirement may be met by either an express or an implicit disclosure (In re Werthein, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976)). The question is whether the concept is present in the original disclosure (In re Anderson, 417 F.2d 1237, 1244, 176 USPQ 331, 336 (CCPA 1973)).

Applicant agrees that knowledge of genes which are expressed in heart tissue, i.e. as recited are expressed in heart tissue and in blood, is required to practice the claimed invention. Applicant contends that this many of these genes are explicity disclosed. In particular, Table 2 of the specification provides a list of over 1800 genes and denotes those which are expressed in heart tissue by the presence of a plus sign (of which there are many). The specification further provides an example of how to measure the expression of genes that were traditionally thought to be tissue specific, such as insulin, ZFP, and ANF. ANF in particular is disclosed as a gene highly expressed in heart tissue (see paragraph [0057]). A person skilled in the art would be able to apply similar experiments to any other of the genes disclosed in Table 2, in addition to applying the same methodology to other genes, identified via similar methods to those disclosed in the specification, or other known methods. The recited concept of identifying in blood biomarkers from this set of genes expressed in heart tissue and blood, is clearly described in the specification. In fact, in addition to ANF, at least two such biomarkers are described in the specification: beta myosin heavy chain and zinc finger protein.

Accordingly, Applicants contend that the specification clearly describes the claimed methods,

In view of the remarks and claim amendments, Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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